Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone

A. Marchesoni, N. Battafarano, M. Arreghini, B. Panni, M. Gallazzi and S. Tosi

Objective. To determine whether patients with early rheumatoid arthritis (RA) treated with cyclosporin A (CsA) and methotrexate (MTX) in combination for 12 months show a lower rate of radiographic deterioration than those treated with MTX alone.

Methods. In this controlled and randomized single-blind trial, 61 consecutive patients with untreated RA of less than 2 yr duration were treated with either CsA + MTX combination therapy (n = 30) or MTX alone (n = 31). The primary end-point was radiographic progression after 12 months, measured using the damage score (DS) of the Sharp and van der Heijde method.

Results. Although there was a significant difference between the mean baseline and 12-month DS in both treatment groups (MTX/CsA, 1.93 ± 0.90; MTX, 7.47 ± 2.03), it was significantly less in the combination arm (P = 0.018). Of the 30 evaluable CsA + MTX patients, 16 (53%) were ACR20 responders, 15 (50%) ACR50 and 14 (47%) ACR70; the corresponding figures in the MTX arm were 19 (61%), 13 (44%) and 6 (19%). Toxicity was acceptable in both groups.

Conclusions. In patients with early RA, CsA + MTX combination therapy led to a significantly lower rate of 12-month radiographic progression, was effective on inflammatory articular symptoms, and was well tolerated.

Key words: Rheumatoid arthritis, Combination therapy, Cyclosporin, Methotrexate.

Traditional therapy with a single disease-modifying anti-rheumatic drug (DMARD) is often insufficient to prevent a poor long-term outcome of rheumatoid arthritis (RA) [1–3], and therefore DMARD combinations are now used widely [4, 5]. Aggressive therapy should rationally be started before the development of any joint damage [6], and this has been confirmed by a number of studies [7–11]. The introduction of the new, very powerful but costly biological agents makes it even more necessary to optimize the use of traditional DMARDs in early RA.

Cyclosporin A (CsA) plus methotrexate (MTX) is one of the most promising DMARD combinations; the mechanisms of action, pharmacokinetics, clinical effects and toxicity profiles of the two drugs suggest that their combination should be additive or synergistic without any overlapping toxicity [12–19].

The aim of this study was to compare the 12-month rate of radiographic progression in patients with early RA treated with CsA plus MTX or with MTX alone.

Patients and methods

Study design

This was a 12-month, controlled, randomized single-blind (the clinical investigator was blinded to the treatment) trial designed to compare the efficacy of CsA plus MTX with that of MTX alone in terms of radiographic progression.
Patient selection

Patients aged 18–65 yr with early (duration < 2 yr) active RA [20] were considered eligible for the study. Active disease was defined as at least six swollen joints, at least eight tender joints, and a Westergren erythrocyte sedimentation rate of ≥30 mm/h in women and ≥20 mm/h in men, or morning stiffness lasting ≥45 min. The exclusion criteria were previous treatment with any DMARD or corticosteroid at a dose of > 10 mg/day, and all clinical conditions, treatments or living habits contraindicating the use of CsA or MTX. Women of childbearing age not using an adequate contraceptive method were also excluded. Before entering the study, all patients were fully informed and gave their written consent.

Therapeutic intervention

The patients were allocated to one of the two treatment arms according to a randomization list, using the sealed envelope procedure. The starting doses were CsA 3 mg/kg/day and MTX 10–15 mg (depending on the patient’s weight), administered intramuscularly once a week. In the case of unwanted effects or poor efficacy, the dose of either drug could be reduced or increased (CsA up to a maximum of 4 mg/kg/day and MTX up to 20 mg/week). Abnormalities in serum creatinine level, arterial pressure and serum transaminases had to be dealt with as recommended by the drug companies. Patients who had to discontinue the therapy before month 12 could be treated with corticosteroids alone (maximum dose 10 mg/day). Only patients who failed on this treatment could be started on other DMARDs.

Concomitant medication

Corticosteroids were allowed but their dose could not exceed 10 mg/day of prednisone or equivalent. Local corticosteroid injections were not allowed in the joints of the hands or feet used to score the radiographic changes.

Efficacy evaluation

The primary end-point was the hand, wrist and foot radiographic damage score (DS), determined using the Sharp method as modified by van der Heijde (scale 0–448) [21]. The secondary end-points were the erosion score (ES), the joint space narrowing score (NS) and the eroded joint count (EJC), calculated using 32 joints. The radiographs were read in paired chronological order by two experienced assessors (AM and MA), who mutually agreed on the score to be assigned to each examined joint.

The clinical and laboratory parameters used to assess the efficacy of the trial medications in treating joint symptoms were those required to define treatment responders on the basis of the ACR criteria [22], including the Italian version of the disability index of the Health Assessment Questionnaire [23].

Safety evaluation

Upon entry to the study, the patients’ medical histories were recorded and the patients underwent chest radiography and electrocardiography. At each visit, they underwent a complete physical and standard laboratory assessment. Possible adverse events were monitored on the basis of spontaneous reports and by asking questions to identify any therapy-related problem that may have occurred since the previous visit.

Statistical analysis

The mean changes (and 95% confidence intervals) between baseline and the end of the trial (month 12) were calculated for all of the radiographic and clinical variables. As these had a normal distribution, within-group comparisons were made using the paired t-test and between-group comparisons by means of the unpaired t-test. The differences in the categorical data were evaluated using the χ² test or Fisher’s exact test as appropriate. The analysis was based on the intention-to-treat approach: in the case of premature trial withdrawal, the clinical data collected at the last protocol visit (last observation carried forward) were used for the clinical evaluation, and the 12-month X-rays were used for the radiographic assessment. Kaplan–Meier and log-rank tests were used to calculate and compare the probabilities of remaining on the study treatments.

In order to evaluate the consistency of the study, the radiographs were read twice at different times. The smallest detectable difference (SDD) was calculated on the basis of the concept of random measurement error and defined as that number greater than the measurement error of progression, as determined by the method of Bland and Altman [24–26].

Results

Thirty of the 61 patients were randomized to the CsA + MTX combination and 31 to MTX alone. Baseline clinical and demographic characteristics of the two groups are shown in Table 1. Of the 30 patients in the CsA + MTX arm, one failed to come to the scheduled visits and seven discontinued the trial treatment because of adverse events. In the MTX group, only two patients discontinued the trial therapy because of adverse events. None of the patients withdrew from the trial because of a poor treatment response. As a result, the probability of survival on treatment was 0.74 for the CsA + MTX group and 0.93 for the MTX group (statistically not significant). None of the patients discontinuing trial treatment received another DMARD before the end of the trial, and their mean corticosteroid dose was only slightly higher than the mean dose of all of the patients (2.3 mg ± 0.46 vs 2.1 mg ± 0.48).

Table 1. Baseline demographic and clinical characteristics of the two treatment groups

<table>
<thead>
<tr>
<th></th>
<th>CsA + MTX (n = 30)</th>
<th>MTX (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)a</td>
<td>46.6 ± 10.5</td>
<td>49.3 ± 10.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female/male</td>
<td>28/2</td>
<td>28/3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of disease (yr)a</td>
<td>0.9 ± 0.7</td>
<td>0.9 ± 0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of swollen jointsa</td>
<td>14.7 ± 7.8</td>
<td>12.5 ± 8.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of tender jointsa</td>
<td>16.1 ± 11.3</td>
<td>15.8 ± 8.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Morning stiffness (min)a</td>
<td>104.5 ± 73.7</td>
<td>99.6 ± 77.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Disability index (HAQ)a</td>
<td>1.3 ± 0.6</td>
<td>1.3 ± 0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>ESR (mm/1st h)a</td>
<td>43.8 ± 22.2</td>
<td>64.7 ± 22.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rheumatoid factor (no. of patients)</td>
<td>19 (63%)</td>
<td>23 (74%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>DAS28a</td>
<td>5.2 ± 1.2</td>
<td>5.1 ± 1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Damage scorea</td>
<td>4.5 ± 6.5</td>
<td>3.1 ± 4.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of eroded jointsa</td>
<td>0.7 ± 1.3</td>
<td>0.8 ± 1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of patients with erosive disease</td>
<td>10 (33%)</td>
<td>12 (39%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

aMean ± s.d. HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; DAS28, Disease Activity Score 28 joints; n.s., not significant.
The mean CsA dose was 2.7 ± 0.3 mg/kg/day at baseline and 2.5 ± 0.6 at the end of the study; the mean baseline doses of MTX were 9.9 ± 0.5 mg/week in the CsA + MTX group and 10.2 ± 0.9 mg/week in the MTX group; the corresponding figures at the end of the study period were 9.5 ± 1.7 and 11.2 ± 3.4 mg/week.

Radiographic evaluation
A complete radiography set was available for 28 patients in the CsA + MTX group and 30 in the MTX group. The mean intra-observer difference (S.D.) in DS progression was 0.7 (2.4), leading to an SDD of 3.4. The changes in the mean values of the DS and the other radiographic scores (ES, NS, EJC) by the end of the trial period are shown in Table 2. Overall, DS progression was more frequent in the MTX group (17 vs 10 patients), but this difference was not statistically significant. However, there was a significant difference in the number of patients whose DS progression was greater than the SDD: five (18%) in the CsA + MTX group and 14 (47%) in the MTX group ($P < 0.04$). Of the 26 patients (13 in each treatment group) with no radiographic alterations at baseline, only two in the CsA + MTX group and four in the MTX group developed structural joint damage. No difference in the changes in radiographic score between patients receiving corticosteroids ($n = 35$) or not ($n = 23$) was recorded.

Clinical evaluation
Of the 30 CsA + MTX patients, 16 (53%) were ACR20 responders, 15 (50%) ACR50 responders and 14 (47%) ACR70 responders; the corresponding figures in the MTX group were 15 (50%) ACR50 responders and 14 (47%) ACR70 responders; the corresponding figures at the end of the study period were 9.5 ± 1.7 and 11.2 ± 3.4 mg/week.

Safety and tolerability
Seven patients (23%) in the CsA + MTX group (four gastrointestinal disturbances, one liver abnormality, one renal dysfunction and one headache) experienced adverse events leading to premature study withdrawal. All of these adverse events resolved quickly after therapy discontinuation, except for the case of breast cancer, which was considered to be unrelated to DMARD treatment. The other adverse events, which occurred in 20 CsA + MTX (67%) and 17 MTX (55%) patients, were well managed by dose reduction and/or co-medication, and were those usually occurring when using CsA and MTX. The mean (S.D.) serum creatinine concentration in the CsA + MTX group was 0.74 (0.13) mg/dl at the start of the study and 0.84 (0.17) mg/dl at the final evaluation (not significant); one patient withdrew from the study because of a 60% increase in creatinine serum over baseline. Arterial hypertension was never responsible for study withdrawal, but required anti-hypertensive therapy in five CsA + MTX patients.

Discussion
The main aim of this study was to verify whether CsA + MTX combination therapy for 12 months had a greater impact on radiographic progression than MTX alone in early RA. The results showed that although radiographic progression occurred in both groups, it was significantly less in the combination arm: the mean DS at the 12-month evaluation was three times higher than at baseline in the MTX group, but only about 40% higher in the CsA + MTX group (Table 2). At patient level, and using the SDD as the cut-off value, definite DS progression was seen in 18% of the CsA + MTX patients and 47% of the MTX patients ($P < 0.04$). Joint deterioration occurred mainly in the patients showing some radiographic alterations at baseline. Analysis of the two DS subscores (ES and NS) showed that the between-group difference in radiographic deterioration was mainly due to the erosive component.

CsA has been shown to be more effective in controlling structural damage than other traditional DMARDs [18] and MTX alone [19], and so the difference in radiographic deterioration between the two trial therapies may well have been due to CsA. On the other hand, other evidence suggests that the effect of CsA on long-term...
radiographic deterioration is not superior to that of parenteral gold [27]. An alternative explanation is that the two agents in the combination may have had additive effects on the mechanisms responsible for structural damage. This seems to be in line with the results of trials showing that early therapy with DMARD combinations may prevent radiographic deterioration more effectively than monotherapies [28, 29]. On the other hand, combined CsA, MTX and intra-articular steroid therapy was shown not to be superior to sulphasalazine alone [30]. Regardless of the mechanisms of action, the results of this study showed that the CsA + MTX combination was quite effective in controlling the 12-month radiographic progression of early RA.

Both trial treatments significantly improved all the clinical and laboratory parameters of disease activity. The rate of ACR20, 50 and 70 responders was not significantly different between the two study groups.

The single-blind design of this study may have influenced the patients’ self-evaluation of disease activity but not the results of the radiographic evaluation, which was carried out blindly. The different number of dropouts in the two treatment groups was another possible bias of this study. As the dropouts were not treated with other DMARDs or higher doses of corticosteroids and as there were markedly more dropouts in the CsA + MTX arm, underestimation of the effect of CsA + MTX may have resulted. Finally, in both treatment groups the mean doses of the study therapies were slightly lower than those established in the protocol. This occurred because therapy doses could be chosen according to the patient’s weight and clinical condition. Higher doses could have a greater impact on radiographic progression, but this remains to be proved.

Safety and tolerability are always an issue when DMARD combinations are used. The rate of treatment discontinuation due to adverse events and the overall number of adverse events were higher in the CsA + MTX arm; however, all the events were easily managed and never considered serious (except for the one case of breast cancer in the MTX group). The much-feared CsA-related renal toxicity occurred in only one case and arterial hypertension in only five cases.

In conclusion, in this study the use of combined CsA and MTX in early RA for 12 months led to a lower rate of radiographic progression than therapy with MTX alone. The efficacies of the two therapies in controlling joint inflammation were similar and, although there were more adverse events in the combination groups, they were easily managed and never serious. Our results suggest that combined CsA and MTX treatment may be more appropriate than MTX monotherapy in patients with potentially aggressive early RA.

Conflict of interest

This was an independent study carried out using only the resources of the hospital. The authors have declared no conflicts of interest.

References


